ARTICLE

Attention-deficit/hyperactivity disorder medication and seizures

Kelsey K. Wiggs, BS, Zheng Chang, PhD, Patrick D. Quinn, PhD, Kwan Hur, PhD, Robert Gibbons, PhD, David Dunn, MD, Isabell Brikell, MSc, Henrik Larsson, PhD, and Brian M. D'Onofrio, PhD

Neurology® 2018;90:e1104-e1110. doi:10.1212/WNL.0000000000005213

Correspondence
Kelsey K. Wiggs
kkwiggs@indiana.edu

CME Course
NPub.org/cmelist

Abstract

Objective

Individuals with attention-deficit/hyperactivity disorder (ADHD) are at increased risk of seizures, but there is uncertainty about whether ADHD medication treatment increases risk among patients with and without preexisting seizures.

Methods

We followed a sample of 801,838 patients with ADHD who had prescribed drug claims from the Truven Health MarketScan Commercial Claims and Encounters databases to examine whether ADHD medication increases the likelihood of seizures among ADHD patients with and without a history of seizures. First, we assessed overall risk of seizures among patients with ADHD. Second, within-individual concurrent analyses assessed odds of seizure events during months when a patient with ADHD received ADHD medication compared with when the same individual did not, while adjusting for antiepileptic medications. Third, within-individual long-term analyses examined odds of seizure events in relation to the duration of months over the previous 2 years patients received medication.

Results

Patients with ADHD were at higher odds for any seizure compared with non-ADHD controls (odds ratio [OR] = 2.33, 95% confidence interval [CI] = 2.24–2.42 males; OR = 2.31, 95% CI = 2.22–2.42 females). In adjusted within-individual comparisons, ADHD medication was associated with lower odds of seizures among patients with (OR = 0.71, 95% CI = 0.60–0.85) and without (OR = 0.71, 95% CI = 0.62–0.82) prior seizures. Long-term within-individual comparisons suggested no evidence of an association between medication use and seizures among individuals with (OR = 0.87, 95% CI = 0.59–1.30) and without (OR = 1.01, 95% CI = 0.80–1.28) a seizure history.

Conclusions

Results reaffirm that patients with ADHD are at higher risk of seizures. However, ADHD medication was associated with lower risk of seizures within individuals while they were dispensed medication, which is not consistent with the hypothesis that ADHD medication increases risk of seizures.

From the Department of Psychological and Brain Sciences (K.K.W., P.D.Q., B.M.D.), Indiana University, Bloomington; Department of Medical Epidemiology and Biostatistics (Z.C., I.B., H.L.), Karolinska Institutet, Stockholm, Sweden; Center for Health Statistics (Z.C., P.D.Q., K.H., R.G.) and Departments of Medicine (R.G.) and Public Health Sciences (R.G.), University of Chicago, IL; Departments of Psychiatry (D.D.) and Neurology (D.D.), Indiana University School of Medicine, Indianapolis; and School of Medical Sciences (H.L.), Orebro University, Sweden.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ADHD = attention-deficit/hyperactivity disorder; **AED** = antiepileptic drug; **CI** = confidence interval; **ICD-9** = *International Classification of Diseases, Ninth Revision*; **OR** = odds ratio.

Comorbidity between attention-deficit/hyperactivity disorder (ADHD) and seizures is more common than expected.[1] One explanation for the co-occurrence is that ADHD medication may induce seizures.[2–13] In fact, the *Physicians' Desk Reference* warns that methylphenidate may lower seizure threshold, resulting in (1) increased seizure frequency among patients with ADHD and seizures, and (2) the occurrence of new-onset seizures among patients with ADHD without a history of seizures.[13]

Studies examining whether exposure to methylphenidate,[2–5,8,11,12] stimulants more broadly,[6] and atomoxetine[7,9] induce seizures are limited by small samples[2–5,7,8,10–12] and an inability to rule out important confounding factors. Past research has also often excluded patients with a seizure history[12] or included patients with an extended seizure-free period,[2,3,12] raising questions about clinical applicability of the findings for patients with seizures. Thus, reviews have concluded that there is not sufficient evidence to judge whether there is short- and long-term harm of ADHD medication for seizures and other rare events.[14–19]

The aim of the current study was to examine concurrent and long-term associations between ADHD medication use and seizures using a large national database of commercial health insurance claims. The sample enabled us to estimate the magnitude of the association among patients with and without a seizure history with precision.[13] Further, we assessed associations within individuals, which eliminates confounding via stable unmeasured factors, and accounted for time-varying covariates, including use of antiepileptic medications.[20–22]

Methods

Sample

We used deidentified inpatient, outpatient, and prescribed drug claims from the Truven Health MarketScan Commercial Claims and Encounters databases. From 2005 to 2014, there were approximately 146 million unique enrollee observations in MarketScan, consisting of employees, COBRA (Consolidated Omnibus Budget Reconciliation Act) continuees, non-Medicare retirees, spouses, and dependents. Analysis of MarketScan is considered exempt human participants' research by the University of Chicago institutional review board.

We included a sample of 801,838 (40.79% female) newly treated patients with ADHD, defined by a diagnosis of ADHD (i.e., ICD-9 code 314.xx) or prescription of ADHD medication following at least 1 year in MarketScan without a diagnosis or prescription. We also selected this incident diagnosis definition to identify those individuals who had no claims for seizures for a least 1 year before the index date. We included ADHD patients aged 5 to 64 years at the initial diagnosis or initiation of medication during 2005–2014; unreliable diagnoses are more likely in younger children.[23] We followed patients with ADHD from their index date (i.e., first diagnosis or prescription fill) until their last month of enrollment or to December 2014. We excluded years in which patients did not have prescription coverage. If patients disenrolled and then reenrolled, we followed them through their first disenrollment. Our sample selection procedure was consistent with prior research using MarketScan data.[24,25]

ADHD medication

We identified ADHD medication using national drug codes from filled prescription claims. Stimulant medications included amphetamine salt combination, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine hydrochloride, methylphenidate, and methylphenidate hydrochloride. We also included atomoxetine hydrochloride, a nonstimulant medication approved to treat ADHD. We defined medication status monthly and medicated months by a prescription receipt that covered at least 1 day during a given month. Of the included patients with ADHD, 526,495 (65.66%) had received at least one prescription (table 1). Most patients received stimulant medication only (88.61%), while a smaller number of patients received atomoxetine only (4.80%) or both types of medications (6.59%).

Seizure events

We defined seizure events as monthly claims for emergency room visits, ambulance rides, or inpatient hospitalizations

Table 1 Summary statistics for included patients with attention-deficit/hyperactivity disorder

	Overall	
Variable	**No.**	**%**
Included patients	801,831	—
Medicated at least once	526,495	65.66
At least one medication switch	413,192	57.52
At least one seizure event	3,163	0.41
Median follow-up, mo (IQR)	16 (9–28)	

Abbreviation: IQR = interquartile range.
Patients with at least one medication status switch had at least 1 month with filled prescription coverage as well as at least 1 month with no prescription coverage.

with ICD-9 codes (345.xx), excluding infantile spasms (345.6x). This operationalization was consistent with that used in prior analyses of MarketScan data,[26–28] and was selected in order to capture time-specific claims rather than ongoing management of seizures. We determined seizure history by *any* inpatient or outpatient claim with a seizure in the database during the 1 year before the index date to increase the likelihood of capturing seizure history.

Data analytic strategy

We made 3 sets of comparisons to assess the association between ADHD medication and seizures among patients with and without a seizure history. We conducted all analyses in SAS 9.4 (SAS Institute Inc., Cary, NC).

Overall risk of seizures among individuals with ADHD

We first examined between-group differences. We used logistic regression to assess the odds of (1) any seizure event among patients with ADHD compared with matched non-ADHD patient controls, (2) any seizure event among patients with ADHD prescribed any medication compared with those who were never prescribed ADHD medication, and (3) any seizure event among patients with ADHD prescribed medication at least once compared with controls. We matched patients with ADHD and controls 1:1 on sex, calendar year, and age of first enrollment in MarketScan, and length of enrollment in months. Our second analysis compared the risk, within the ADHD patient group, of any seizure during medicated months relative to unmedicated months, adjusted for sex, calendar year, age of first enrollment in MarketScan, and length of enrollment in months.

Concurrent association of ADHD medication with seizures

Second, we assessed concurrent associations between ADHD medication and seizure events among patients with and without a seizure history. We structured follow-up time by months and used discrete-time logistic regression models.[29] When new prescriptions for ADHD medication and seizures occurred in the same month (n = 100), we coded months as medicated if the seizure occurred after the date of the prescription fill (n = 51) and nonmedicated if the seizure occurred before or on the date of the prescription fill (n = 49). For analyses including patients with a seizure history, we permitted repeated events during follow-up. However, we limited follow-up to first events in the analyses including patients with no seizure history, because once these patients had a recorded seizure event, they should no longer be defined as such. This analysis also helps rule out reverse causation, as having a seizure may decrease the subsequent likelihood of being prescribed ADHD medication because of perceived seizure risk.

We began with population-level models, which assessed the odds of seizure events during medicated months compared with unmedicated months while adjusting for sex and the following measured time-varying covariates: age, calendar year, and prescription of antiepileptic drugs (AEDs) (see table e-1, links.lww.com/WNL/A291, for included AEDs). Repeated-events, population-level models also adjusted for time since last seizure event and the nonindependence of observed months within individuals (PROC SURVEYLOGISTIC). The models, however, could not account for unmeasured factors that differ between patients who did and did not receive ADHD medication.

For our primary analyses, we used conditional logistic models to compare medicated and nonmedicated months *within individuals* to assess the association independent of stable confounding factors while also adjusting for the time-varying covariates (i.e., AED medication and time since last seizure for repeated-events models). These models compared seizure risk during periods when an individual received medication relative to when the same individual did not receive medication. Because each individual serves as his/her own control, this approach accounts for all unmeasured factors that are stable within the individual (e.g., general severity of ADHD, genetic predisposition for ADHD and/or seizures, general seizure liability).

We conducted 6 sensitivity analyses to test the robustness of our findings among all patients with ADHD, without stratification for seizure history. First, we analyzed the association with stimulant medication only because all stimulants have similar mechanisms of action (i.e., increased available dopamine),[14] whereas atomoxetine is a norepinephrine reuptake inhibitor.[16] Second, we considered whether additional psychotropic medications may be confounding the association by examining the association by excluding persons with psychotropic medication prescriptions, including an AED prescription. Third, we conducted an analysis extending ADHD medication exposure by 1 month to provide a more conservative estimate of medication discontinuation. Fourth, we considered the possibility that our outcome definition was capturing the same event multiple times. To address this, we restricted seizure events to emergency room visits only for a more conservative index of seizure events. Fifth and sixth, we conducted analyses separately by sex and among various age groups to assess whether the associations differ by sex or among patients of different ages.

Cumulative long-term association of ADHD medications with seizures

Third, to examine whether long-term ADHD medication receipt was associated with seizure risk, we examined the association between the cumulative number of prescribed months across 2 years and subsequent seizure events. Similar to concurrent analyses, we began with population-level models, but our primary analyses examined the association within individuals. We included concurrent medication status in all models to assess the cumulative association independent of current medication effects. Our population-level models also adjusted for age, sex, calendar year, time since last seizure, and AED prescription; within-individual models adjusted for

time since last seizure event and AED prescription. Patients included in analyses had 2 years of follow-up time. Months prior to 2 years of follow-up were excluded. We conducted similar sensitivity analyses as outlined above. We also examined a 3-year cumulative association, as well as the association between ADHD medication and subsequent seizure events 2 and 3 years later.

Results

Overall risk of seizures among individuals with ADHD

Demographic information is presented in table 1. We identified 474,742 (59.21%) male and 327,089 (40.79%) female patients with ADHD. Median age at follow-up was 17 years (interquartile range, 8–36). Of the 801,838 identified patients with ADHD, we were able to match 801,831 with controls.

We present group comparisons in table e-2 (links.lww.com/WNL/A291). Among patients with ADHD, 1.84% of male and 2.06% of female patients had at least one seizure event, compared with 0.80% of male and 0.90% of female controls (odds ratio [OR] 2.33, 95% confidence interval [CI] 2.24–2.42 males; OR 2.31, 95% CI 2.22–2.42 females). In ever-medicated patients with ADHD, 1.44% of males and 1.63% of females had at least one seizure, compared with 2.14% of male and 2.58% of female never-medicated patients with ADHD (OR 0.63, 95% CI 0.60–0.67 males; OR 0.61, 95% CI 0.57–0.64 females). Finally, male and female ever-medicated patients with ADHD were at higher odds of any seizure event compared with controls (OR 1.69, 95% CI 1.59–1.80 males; OR 1.61, 95% CI 1.52–1.71 females).

Concurrent association of ADHD medication with seizures

Adjusted concurrent associations are presented in table 2. In the adjusted population-level models, medicated months were associated with 43% lower odds of seizure events among ADHD patients with a history of seizures. Among patients without a seizure history followed up to first events, medicated periods were associated with 40% lower odds of seizure events relative to unmedicated periods. More importantly, in our within-individual comparisons, patients with a seizure history were at 29% lower odds of seizure events during the months in which they were medicated compared to non-medication periods. Similarly, patients with no recorded prior seizures were at 49% lower odds of a seizure event during periods in which an individual was medicated compared to when the same individual was not. Sensitivity analyses examining the association between ADHD medication and seizures in various subcohorts and by varying the definition of exposure and outcome provided commensurate results with the main analyses (table 3).

We present point estimates for the inclusion of AEDs as a time-varying covariate in our concurrent analyses in table e-3 (links.lww.com/WNL/A291). Overall, AED medication prescription receipt was associated with increased risk of seizure events. However, we do not take this to mean that AED medication caused seizures. Rather, this association likely reflects reverse causation, as individuals' seizure status and the ongoing management of seizures are likely responsible for the positive association.

Table 2 Adjusted concurrent associations between attention-deficit/hyperactivity disorder medication and seizures

Cohort	No. of patients	No. of seizures	Population-level	Within-individual
Repeated events				
With any prior seizure	9,739	2,890	0.57 (0.50–0.64)	0.71 (0.60–0.85)
First events				
With no prior seizure	792,099	1,675	0.60 (0.54–0.67)	0.51 (0.43–0.62)

Data represent count or odds ratio (95% confidence interval). The population models control for age, sex, calendar year, time since last seizure event, and antiepileptic drug prescription. Within-individual models control for time since last seizure event and antiepileptic drug prescription.

Table 3 Adjusted concurrent within-individual sensitivity analyses

Sensitivity analyses (within only)	No. of patients	No. of seizures	OR (95% CI)
Repeated events			
Stimulant only	801,838	5,427	0.74 (0.66–0.82)
No other psychotropic medications	453,356	246	1.03 (0.57–1.86)
1-mo extended	801,838	5,427	0.72 (0.65–0.81)
ER only	801,838	3,539	0.81 (0.71–0.92)
Men only	474,744	3,105	0.68 (0.59–0.78)
Women only	327,094	2,322	0.74 (0.63–0.87)
Age group, y			
5–6	81,089	873	0.95 (0.73–1.23)
7–12	223,045	1,345	0.68 (0.55–0.83)
13–17	130,535	1,156	0.57 (0.44–0.72)
18–25	144,115	910	0.88 (0.66–1.16)
26–35	78,188	396	0.53 (0.37–0.76)
36–45	73,491	374	0.58 (0.38–0.89)
46+	71,375	373	0.79 (0.48–1.31)

Abbreviations: CI = confidence interval; ER = emergency room; OR = odds ratio.
Within-individual models control for time since last seizure event and antiepileptic drug prescription (excluding the no other psychotropic medication analysis).

Table 4 Adjusted long-term cumulative associations between ADHD medication and seizures

Cohort	No. of patients	No. of seizures	Population-level		Within-individual	
			Long-term	Concurrent	Long-term	Concurrent
Cumulative duration						
Any prior seizure	3,480	805	0.88 (0.74–1.03)	0.79 (0.62–1.01)	0.87 (0.59–1.30)	0.79 (0.55–1.15)
No prior seizure	301,847	1,176	0.94 (0.82–1.08)	0.69 (0.55–0.87)	1.01 (0.80–1.28)	0.67 (0.53–0.85)

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.
Data represent count or odds ratio (95% confidence interval). Cumulative associations are the odds of events predicted by the cumulative number of months medicated during the 2 years prior. Adjusted population models adjust for current ADHD medication status, age, sex, calendar year, time since last seizure event, and antiepileptic drug prescription. Within-individual models adjust for current ADHD medication status, time since last seizure event, and antiepileptic drug prescription.

Cumulative long-term association of ADHD medications with seizures

Next, we analyzed 2-year cumulative associations between ADHD medication and seizure events (table 4). In the population-level models, 2-year duration of medication was not associated with seizure events among patients with and without prior seizures. Our within-individual estimates produced similar results. In addition, varying our cohort, exposure, and outcome definitions produced similar findings (table 5). We present the point estimates for the inclusion of AEDs as a time-varying covariate in our long-term analyses in table e-4 (links.lww.com/WNL/A291). Again, point estimates likely reflect ongoing management of seizures requiring AED medication.

Discussion

The results of this study are not consistent with the hypothesis that ADHD medication increases seizure frequency and/or induces new seizures in patients concurrently. Furthermore, we found no evidence that long-term cumulative duration of ADHD medication increases risk of seizures. Our findings substantially expand on the current literature. Our use of large insurance claims data allowed us to more precisely test the association between ADHD medication and seizures while using a design feature (i.e., within-individual comparisons) to adjust for unmeasured confounding factors that are typically unadjusted for by traditional between-individual comparisons. We provide converging evidence with the body of literature that has not found increased risk of seizures due to ADHD medication,[2–4,6–9,11,12] as well as one preliminary study that has suggested that ADHD medication is associated with decreased risk of seizures.[30] Furthermore, we were able to specifically examine whether the association between ADHD medication and risk of seizures differs among patients with and without a seizure history. Individuals with a history are perceived to be most at risk of worsening of seizures as a result of ADHD medication, and our outcome definition

Table 5 Adjusted long-term cumulative and interval within-individual sensitivity analyses

Sensitivity analyses (within only)	No. of patients	No. of seizures	Long-term	Concurrent
Cumulative duration				
3 y	193,612	1,246	1.06 (0.86–1.31)	0.68 (0.52–0.88)
Stimulant medication only	305,327	1,981	0.96 (0.78–1.17)	0.77 (0.63–0.95)
No other psychotropic medications	155,386	49	1.60 (0.41–6.30)	2.79 (0.60–12.97)
ER only	305,327	1,403	0.88 (0.69–1.11)	0.77 (0.61–0.98)
Men only	184,172	1,154	0.97 (0.74–1.27)	0.66 (0.50–0.86)
Women only	121,155	827	0.98 (0.73–1.32)	0.76 (0.56–1.02)
Time interval, y				
3	193,612	1,246	1.07 (0.88–1.31)	0.69 (0.53–0.89)
2	305,327	1,981	0.95 (0.80–1.11)	0.69 (0.57–0.84)

Abbreviation: ER = emergency room.
Data represent count or odds ratio (95% confidence interval). Adjusted models adjust for current attention-deficit/hyperactivity disorder medication status, time since last seizure event prescription of antiepileptic drugs. Cumulative associations are the odds of events predicted by the cumulative number of months medicated during the 2 or 3 years prior. Interval associations are the odds of events predicted by medication status 2 or 3 years prior.

likely captures particularly severe events (as they warranted emergency or inpatient treatment). As such, the results do not support the hypothesis that ADHD medication is responsible for the comorbidity between ADHD and seizures. That is, we found no evidence of increased risk of seizures as a result of ADHD medication, regardless of seizure history.

There are several possible explanations for the finding that ADHD medication was associated with lower odds of seizure occurrence. If our findings reflect real protective effects of ADHD medication, one explanation for lower risk may be that ADHD medication treats symptoms of a shared mechanism putting individuals at risk of both ADHD and seizures.[9,10,31–33] ADHD medication may also influence seizures via increased AED compliance or reduction of precipitating factors, such as stress.[34] An alternative explanation for our findings is that individuals with seizures are not given ADHD medication because of the concern that it may worsen their condition. ADHD medication was associated with lower odds of the occurrence of the *first* seizure event among patients without previous seizures, which may help rule out this possibility. However, it is possible that individuals may have had seizure events not recorded in our data, and we were not able to examine whether physicians refrained from prescribing ADHD medication to individuals with more severe seizures. Future research will need to study these factors more closely.

The comorbidity between ADHD and seizures may partially explain concern surrounding ADHD medication, as physicians are more likely to see seizure occurrence in individuals with ADHD.[2–9] This, taken together with our concurrent and long-term findings, suggests that other factors may explain the association between ADHD medication and seizures. These findings are consistent with multiple hypotheses for why ADHD co-occurs with seizures/epilepsies. First, the comorbidity may reflect a distinct or severe neurologic disorder[18,31]; individuals with comorbid ADHD and seizures have more severe symptoms compared with individuals with one diagnosis.[29] Second, a shared underlying biological vulnerability or cause may account for the comorbidity, including common genetic[32] or environmental factors (e.g., CNS injury)[35] that lead individuals to develop both ADHD and seizures. Third, the comorbidity may be attributable to the influence of one disorder on another.[36] Specifically, ADHD symptoms may be a consequence of seizures, either due to added brain insult via seizures[31] or due to AED-induced ADHD symptoms in patients with seizures.[37] Alternatively, ADHD may put an individual at risk for CNS injury and, therefore, seizures.[35]

Our findings are subject to several limitations. First, because we used an observational design, we cannot draw definitive causal conclusions; time-varying factors that were not measured or measured imperfectly may still confound the association. For example, we cannot rule out the possibility that the findings reflect an association with general treatment engagement. In contrast to previous studies that used other psychotropic medications as a negative control to address this concern,[20–22,25] we were unable to do so because such medications are known to be associated with seizure activity.[38–40] Second, atomoxetine was the only included nonstimulant ADHD medication; we did not explore atomoxetine alone because the majority of research has focused specifically on stimulant medications. Third, we examined the association among patients with commercial health insurance in the United States. We do not know how well our findings will generalize to other populations (i.e., lack of insurance, Medicaid, Medicare) and other countries. Fourth, measurement error regarding our exposure and outcome may have biased our findings. Given that our data come from health insurance claims, we cannot ensure medication compliance (i.e., if and how frequently individuals who picked up their prescription actually took their medication), and we do not know whether individuals received medication not covered by insurance. Our measure of seizure events (i.e., emergency department, ambulance rides, and inpatient hospitalizations) and history of seizures (i.e., *any* inpatient or outpatient seizure claims) may not have captured all seizures. As such, we cannot ensure that individuals identified to have no prior seizures may have actually had seizures that were not captured in our data, and seizure events that are captured are likely representative of more severe seizures and/or epilepsies. It is important to note, however, that nondifferential misclassification would attenuate the associations, making the results and our conclusions more conservative. Fifth, we were not able to differentiate between seizure-free patients with ADHD who do and do not have epileptiform EEG patterns. Future research should address this; however, previous data have suggested no difference among these groups.[6]

In sum, using a large commercial health insurance claims database to examine the association between ADHD medication and risk of seizures in a cohort of ADHD patients with and without a history of seizures, we observed lower risk of seizures within individuals during medication periods compared to nonmedication periods. While we do not take this to mean that ADHD medication should be used as a treatment for seizures, our findings suggest that concerns about ADHD medication causing seizures should be mitigated as physicians and patients weigh risks and benefits of these medications.

Author contributions

Kelsey K. Wiggs: secured funding, analytic design, writing, and revisions. Zheng Chang: analytic design, data analysis, and revisions. Patrick D. Quinn: secured funding, analytic design, and revisions. Kwan Hur: analytic design and revisions. Robert Gibbons: supervision and revisions. David Dunn: supervision and revisions. Isabell Brikell: analytic design and revisions. Henrik Larsson: secured funding, analytic design, supervision, and revisions. Brian M. D'Onofrio: secured funding, analytic design, supervision, and revisions. Zheng Chang had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study funding

This project was supported by NIMH grant R01MH102221, NIH grant T32HD07475, and NIDA grant K99DA040727. MarketScan is a registered trademark of Truven Health Analytics Inc.

Disclosure

K. Wiggs, Z. Chang, P. Quinn, and K. Hur report no disclosures relevant to the manuscript. R. Gibbons has served as an expert witness in cases involving the US Department of Justice and Wyeth, Pfizer, and GlaxoSmithKline pharmaceutical companies. D. Dunn and I. Brikell report no disclosures relevant to the manuscript. H. Larsson has served as a speaker for Eli Lilly and Shire and has received research grants from Shire, all outside the submitted work. B. D'Onofrio reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Received July 31, 2017. Accepted in final form December 12, 2017.

References

1. Bertelsen EN, Larsen JT, Petersen L, Christensen J, Dalsgaard S. Childhood epilepsy, febrile seizures, and subsequent risk of ADHD. Pediatrics 2016;138:e20154654.
2. Feldman H, Crumrine P, Handen BL, Alvin R, Teodori J. Methylphenidate in children with seizures and attention-deficit disorder. Am J Dis Child 1989;143:1081–1086.
3. Gonzalez-Heydrich J, Whitney J, Waber D, et al. Adaptive phase I study of OROS methylphenidate treatment of attention deficit hyperactivity disorder with epilepsy. Epilepsy Behav 2010;18:229–237.
4. Gross-Tsur V, Manor O, Van der Meere J, Joseph A, Shalev R. Epilepsy and attention deficit hyperactivity disorder: is methylphenidate safe and effective? J Pediatr 1997;130:670–674.
5. Gucuyener K, Erdemoglu AK, Senol S, Serdaroglu A, Soysal S, Kockar I. Use of methylphenidate for attention-deficit hyperactivity disorder in patients with epilepsy or electroencephalographic abnormalities. J Child Neurol 2003;18:109–112.
6. Hemmer SA, Pasternak JF, Zecker SG, Trommer BL. Stimulant therapy and seizure risk in children with ADHD. Pediatr Neurol 2001;24:99–102.
7. Torres A, Whitney J, Rao S, Tilley C, Lobel R, Gonzalez-Heydrich J. Tolerability of atomoxetine for treatment of pediatric attention-deficit/hyperactivity disorder in the context of epilepsy. Epilepsy Behav 2011;20:95–102.
8. van der Feltz-Cornelis C, Aldenkamp A. Effectiveness and safety of methylphenidate in adult attention deficit hyperactivity disorder in patients with epilepsy: an open treatment trial. Epilepsy Behav 2006;8:659–662.
9. Wernicke JF, Holdridge KC, Jin L, et al. Seizure risk in patients with attention-deficit-hyperactivity disorder treated with atomoxetine. Dev Med Child Neurol 2007;49:498–502.
10. Wroblewski BA, Leary JM, Phelan AM, Whyte J, Manning K. Methylphenidate and seizure frequency in brain injured patients with seizure disorders. J Clin Psychiatry 1992;53:86–89.
11. Adams J, Alipio-Jocson V, Inoyama K, et al. Methylphenidate, cognition, and epilepsy: a double-blind, placebo-controlled, single-dose study. Neurology 2017;88:470–476.
12. Rheims S, Herbillon V, Villeneuve N, et al. ADHD in childhood epilepsy: clinical determinants of severity and of the response to methylphenidate. Epilepsia 2016;57:1069–1077.
13. PDR Staff. Physicians' Desk Reference, 71st ed. Montvale: PDR Network; 2017.
14. Chan E, Fogler JM, Hammerness PG. Treatment of attention-deficit/hyperactivity disorder in adolescents: a systematic review. J Am Med Assoc 2016;315:1997–2008.
15. Shaw P. Quantifying the benefits and risks of methylphenidate as treatment for childhood attention-deficit/hyperactivity disorder. J Am Med Assoc 2016;315:1953–1955.
16. Storebø OJ, Krogh HB, Ramstad E, et al. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents: cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials. BMJ 2015;351:h5203.
17. Gonzalez-Heydrich J, Weiss M, Connolly M, et al. Pharmacological management of a youth with ADHD and a seizure disorder. J Am Acad Child Adolesc Psychiatry 2006;45:1527–1532.
18. Dunn DW, Kronenberger WG. Is ADHD in epilepsy the expression of a neurological disorder? In: Kanner A, Schachter SC, editors. Psychiatric Controversies in Epilepsy. Cambridge: Academic Press; 2010:141.
19. Dunn DW, Kronenberger WG. Childhood epilepsy, attention problems, and ADHD: review and practical considerations. Semin Pediatr Neurol 2005;12:222–228.
20. Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS, Simonsen M. Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. Lancet Psychiatry 2015;2:702–709.
21. Lichtenstein P, Halldner L, Zetterqvist J, et al. Medication for attention deficit–hyperactivity disorder and criminality. N Engl J Med 2012;367:2006–2014.
22. Chang Z, Lichtenstein P, Halldner L, et al. Stimulant ADHD medication and risk for substance abuse. J Child Psychol Psychiatry 2014;55:878–885.
23. Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2007;46:894–921.
24. Chang Z, Lichtenstein P, D'Onofrio BM, Sjölander A, Larsson H. Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. JAMA Psychiatry 2014;71:319–325.
25. Quinn PD, Chang Z, Hur K, et al. ADHD medication and substance-related problems. Am J Psychiatry 2017;174:877–885.
26. Faught E, Helmers SL, Begley CE, et al. Newer antiepileptic drug use and other factors decreasing hospital encounters. Epilepsy Behav 2015;45:169–175.
27. Hansen RN, Campbell JD, Sullivan SD. Association between antiepileptic drug switching and epilepsy-related events. Epilepsy Behav 2009;15:481–485.
28. Hansen RN, Nguyen HP, Sullivan SD. Bioequivalent antiepileptic drug switching and the risk of seizure-related events. Epilepsy Res 2013;106:237–243.
29. Efron B. Logistic regression, survival analysis, and the Kaplan-Meier curve. J Am Stat Assoc 1988;83:414–425.
30. Santos K, Palmini A, Radziuk AL, et al. The impact of methylphenidate on seizure frequency and severity in children with attention-deficit–hyperactivity disorder and difficult-to-treat epilepsies. Dev Med Child Neurol 2013;55:654–660.
31. Sherman E, Slick DJ, Connolly MB, Eyrl KL. ADHD, neurological correlates and health-related quality of life in severe pediatric epilepsy. Epilepsia 2007;48:1083–1091.
32. Dunn DW, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. Dev Med Child Neurol 2003;45:50–54.
33. Pettersson E, Anckarsäter H, Gillberg C, Lichtenstein P. Different neurodevelopmental symptoms have a common genetic etiology. J Child Psychol Psychiatry 2013;54:1356–1365.
34. Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav 2005;6:85–89.
35. Gerring JP, Brady KD, Chen A, et al. Premorbid prevalence of ADHD and development of secondary ADHD after closed head injury. J Am Acad Child Adolesc Psychiatry 1998;37:647–654.
36. Kaufmann R, Goldberg-Stern H, Shuper A. Attention-deficit disorders and epilepsy in childhood: incidence, causative relations and treatment possibilities. J Child Neurol 2009;24:727–733.
37. Austin JK, Harezlak J, Dunn DW, Huster GA, Rose DF, Ambrosius WT. Behavior problems in children before first recognized seizures. Pediatrics 2001;107:115–122.
38. Kanner AM. Management of psychiatric and neurological comorbidities in epilepsy. Nat Rev Neurol 2016;12:106–116.
39. Alper K, Schwartz KA, Kolts RL, Khan A. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry 2007;62:345–354.
40. Bhattacharyya S, Darby RR, Raibagkar P, Castro LNG, Berkowitz AL. Antibiotic-associated encephalopathy. Neurology 2016;86:963–971.

FULL-LENGTH ARTICLE NPub.org/0bs4jj

Attention-deficit/hyperactivity disorder medication and seizures

Kelsey K. Wiggs, BS, Zheng Chang, PhD, Patrick D. Quinn, PhD, Kwan Hur, PhD, Robert Gibbons, PhD, David Dunn, MD, Isabell Brikell, MSc, Henrik Larsson, PhD, and Brian M. D'Onofrio, PhD

Correspondence
K.K. Wiggs
kkwiggs@indiana.edu

Cite as: *Neurology*® 2018;90:e1104-e1110. doi:10.1212/WNL.0000000000005213

Study question

Do medications for attention-deficit/hyperactivity disorder (ADHD) increase the risk of seizures?

Summary answer

ADHD medications do not increase the risk of seizures.

What is known and what this paper adds

The prevalence of seizures in people with ADHD is higher than expected, and some researchers have therefore hypothesized that ADHD medications increase the risk of seizures. However, this study provides evidence against that hypothesis.

Participants and setting

This study examined data for 801,838 patients with newly treated ADHD and 801,831 age-, sex-, and year-matched healthy controls. These data came from the 2005–2014 period of the Truven Health MarketScan Commercial Claims and Encounters databases.

Design, size, and duration

The study analyzed the overall risk of seizures among ADHD patients relative to matched controls, the risk of seizures while ADHD patients were prescribed ADHD medications, and the long-term risk of seizures following treatment with ADHD medications. Importantly, analyses examined risk of ADHD medication between medicated months and un-medicated months in the population, as well as when the same individual was medicated and un-medicated.

Primary outcomes

The primary outcome was a seizure event, as reflected in monthly claims for seizure-related emergency room visits, ambulance rides, and hospitalizations.

Main results and the role of chance

Of the participants, 526,495 (65.66%) received at least one prescription. Compared to sex-matched healthy controls, the occurrence of at least one seizure event was more common in both male (odds ratio [OR], 2.33; 95% CI, 2.24–2.42) and female patients (OR, 2.31; 95% CI, 2.22–2.42). Within-individual analyses showed that the risk of seizures was lower in on-medication months than in off-medication months both in patients with prior seizures (OR, 0.71; 95% CI, 0.60–0.85) and in patients without such histories (OR, 0.51; 95% CI, 0.43–0.62). However, no long-term associations between ADHD medication usage and seizure events were found.

	Population-level long-term OR (95% CI)	Within-individual long-term OR (95% CI)
Patients with prior seizures	0.88 (0.74–1.03)	0.87 (0.59–1.30)
Patients without prior seizures	0.94 (0.82–1.08)	1.01 (0.80–1.28)

Bias, confounding, and other reasons for caution

The study's observational nature precluded detection of causal relationships. Atomoxetine was the only nonstimulant ADHD medication examined. The data might not have reflected all seizure events.

Generalizability to other populations

The study only examined persons in the US with commercial health insurance. This may limit generalizability to US persons without commercial health insurance and to persons in other countries.

Study funding/potential competing interests

This study was funded by the NIH. Dr. Gibbons has served as an expert witness in trials involving pharmaceutical companies. Dr. Larson has served as a speaker for Eli Lilly and Shire and received research grants from Shire. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

